بسم الله الرحمن الرحيم

"و في أنفسكم أفلا تبصرون"

صدق الله العظيم

Uremic Toxins
The Known and The Unknown

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INTRODUCTION

The uremic syndrome

- The deterioration of multiple biochemical and physiological functions in parallel with progressive renal failure resulting in complex but variable symptomatology .

- Uremic retention solutes accumulate in the patient with chronic kidney disease (CKD), including the patient with K/DOQI stage 5 disease or end-stage renal disease (ESRD).

- ***Uremic toxins*** can be subdivided into three major groups based upon their chemical and physical characteristics:

1. Small, water-soluble, non-protein-bound compounds, such as urea

2. Small, lipid-soluble and/or protein-bound compounds, such as the phenols

3. Larger so-called middle-molecules, such as beta2-microglobulin

A) SMALL WATER-SOLUBLE COMPOUNDS

1) Urea

- Urea inhibits Na-K-2Cl cotransport in human erythrocytes.
- Urea inhibits macrophage-inducible nitric oxide synthesis
- Urea may provoke dialysis disequilibrium if the decrease in plasma concentration of urea during dialysis occurs too rapidly.
- Urea is a precursor of some of the guanidines which induce biochemical alterations by themselves.
- Increasing amounts of cyanate are spontaneously transformed from urea.

- Marker of dialysis adequacy. Thus, urea kinetic modeling is one of the principal tools to currently estimate and (if necessary) correct the dialysis dose.

- However, high blood concentrations of urea may not necessarily correlate with poor outcome:

1. High serum concentrations of urea due to adequate protein intake that are compensated by adequate removal may be relatively harmless, as compared with high urea levels due to inadequate dialysis .

2. Low urea levels related to low protein intake may negatively correlate with prognosis .

- The dialytic removal of lipophilic protein-bound compounds, as well as that of several other water soluble compounds, is different from that of urea.

- Therefore, there should be a search for marker molecules that are representative of large and/or lipid-soluble compounds ***(B2-microglobulin).***

2) Guanidines

- Inhibit neutrophil superoxide production .
- Exert both pro- and anti-inflammatory effects upon leukocytes.
- Induce seizures after systemic and/or cerebroventricular administration in animals.
- Suppress the natural killer cell response.
- Cause structural damage to proteins which in turn reduces the binding of homocysteine

- **Nitric oxide and guanidines**

1. Nitric oxide (NO) synthesis is inhibited in patients with ESRD.

2. Inhibitors include ADMA, SDMA,

3. ***Asymmetric dimethylarginine*** (ADMA), most specific. In the brain, ADMA causes vasoconstriction and inhibition of acetylcholine-induced vasorelaxation. It has also been implicated in the development of hypertension and adverse cardiovascular events .

4. ***Symmetric dimethylarginine*** (SDMA) was linked to an increase in reactive oxygen production.

3) Oxalate

- Among ESRD patients , serum oxalate concentrations are increased approximately **40-fold**, compared with healthy controls . Secondary oxalosis in such patients is characterized by the deposition of calcium oxalate in multiple tissues.

- Currently, such findings may be seen among those with excessive intake of oxalate precursors and those with inflammatory bowel disease.

- In hemodialysis patients, pyridoxine at 800 mg/day causes a decrease in oxalate concentration. However, such high doses of pyridoxine may induce gastrointestinal intolerance.

- Dialytic removal of oxalate is similar to that of urea and, therefore, is relatively easy with any of the classic dialysis strategies.

4) Phosphorus

- A high serum concentration of phosphates is clearly related to pruritus and hyperparathyroidism. Phosphorus excess also inhibits 1 alpha-hydroxylase and hence the production of calcitriol.

- Phosphorus retention causes intestinal dysfunction and proliferation of intestinal villi.

- Blood phosphorus concentration is the result of protein catabolism and protein intake as well as of the ingestion of other dietary sources. Restriction of oral protein intake increases the risk of malnutrition which can be avoided by the administration of oral phosphate binders (Sevelamer).

- One major effect related to hyperphosphatemia is the increase in serum Ca x P product resulting in Ca deposition in the tissues, especially the vessel wall. Application of calcium containing intestinal phosphate binders may decrease P, but this effect is counterbalanced by a rise in Ca and an unmodified Ca x P product.

- Dialytic removal of phosphate is unpredictable and often followed by impressive rebounds, which is due to the release of intracellular phosphate stores.

- Slower dialysis techniques may allow a better control of phosphate levels.

5) Metabolic acidosis —Metabolic acidosis can cause muscle wasting and bone mineral loss and, in children, impair growth.

6) Creatinine — Although serum creatinine is a marker for renal function, only limited data suggest that this substance is associated with adverse effects.

7) Polyamines — Polyamines, which are measured at increased levels in uremia, may contribute to anorexia, vomiting, and adverse central nervous system effects.

B) PROTEIN-BOUND COMPOUNDS

1) P-cresol and p-cresylsulfate —Because of their strong protein binding, their removal by classical dialysis is hampered, therefore alternative removal methods (eg, adsorption or convective transport) should be developed before adequate elimination of these toxins can be obtained.

- High-flux dialysis, compared to low-flux dialysis, has no beneficial effect on the removal of these toxins. However, compared with peritoneal dialysis, p-cresol is cleared better with high-flux hemodialysis.

- P-cresol is an end-product of protein catabolism, produced by intestinal bacteria that metabolize tyrosine and phenylalanine. Environmental sources of p-cresol are toluene, menthofuran (in several herbal medicines, flavoring agents) and cigarette smoke.

- p-cresylsulfate stimulated baseline leukocyte activity, thereby pointing to a pro-inflammatory effect, whereas the parent compound p-cresol essentially inhibits activated leukocyte function and both may alter endothelial function.

- By applying combined fractionated plasma separation and adsorption, removal of p-cresol could be markedly enhanced, a strategy currently used as an artificial liver. Unfortunately, the approach applied in this study resulted in major coagulation disturbances.

- There are studies in animals suggesting that intestinal bacterial production and intestinal uptake of p-cresol can be altered. As an example, prevention of the intestinal absorption of p-cresol by administration of oral sorbents decreased its serum concentration.

2) Homocysteine — (Hcy) is a sulphur-containing amino acid produced by the demethylation of methionine.

- Its retention with uremia results in the cellular accumulation of S-adenosyl homocysteine (AdoHcy), an extremely toxic compound that competes with S-adenosyl-methionine (AdoMet) and inhibits methyltransferases.

- Hyperhomocysteinemia also disturbs gene expression . Guanidino compounds modify serum albumin in a way that protein binding of homocysteine is decreased.

- Patients with chronic renal failure have total serum Hcy levels two- to fourfold above those observed in normal individuals.

- Hcy increases the proliferation of vascular smooth muscle cells, one of the most prominent hallmarks of atherosclerosis. Hcy also disrupts several vessel wall-related anticoagulant functions, resulting in enhanced thrombogenicity

- Hcy levels can be moderately reduced by the administration of folic acid, vitamin B6, and/or vitamin B12. To reduce Hcy, patients with ESRD may require higher quantities of vitamins than the nonuremic population.

- Dialytic removal of Hcy is thought to be hampered in a similar way as the other protein-bound uremic toxins. Dialysis with the extremely open ("super flux") dialysis membranes, however, could decrease homocysteine concentrations, possibly due to a modification of metabolism, rather than to direct removal.

3) Indoles

- Indoxyl sulfate is metabolized by the liver from indole, which is produced by the intestinal flora as a metabolite of tryptophan.

- Indoxyl sulfate, which is secreted in the normal kidney by organic anion transporter 3, enhances drug toxicity by competition with acidic drugs at protein binding sites and inhibits the active tubular secretion of these compounds as well as the deiodination of (T4).

- Indoxyl sulfate may cause a faster progression of glomerular sclerosis and renal failure by inducing free radical production, and upregulation of plasminogen activator inhibitor-1 (PAI-1) expression .

- Indoxyl sulfate may play a role in inhibiting endothelial cell proliferation and repair.

- It has been suggested that indoxyl sulfate plays a role in aortic calcification and elements of bone dysfunction, such as osteoblast dysfunction.

- Removal of protein-bound indoles is hampered during dialysis, superflux membrane was superior to low flux one. In a group of CKD patients not yet on dialysis, the adsorbent AST-120 (Kremezin R) actively decreased indoxyl sulfate in a dose dependent way.

- Oral administration of bifidobacteria (probiotic) in gastro-resistant capsules modifying intestinal flora to hemodialysis patients reduces serum levels of indoxyl sulfate by correcting gastrointestinal flora.

4) Furanpropionic acid (FPA)

- A major inhibitor of drug protein binding, causes a decrease in renal excretion of various drugs, metabolites, and endogenously produced organic acids.

- FPA also inhibits hepatic glutathione-S-transferase, deiodination of T4.

- There is a correlation between neurologic abnormalities and the plasma concentration FPA .

- Since FPA is virtually 100 percent protein-bound, its removal by hemodialysis strategies is virtually nonexistent. FPA levels can be lowered substantially only with peritoneal dialysis.

C) MIDDLE MOLECULES

- Middle molecules, arbitrarily defined as those of a molecular weight (MW) in excess of 500 D.
- Chromatographic fractions of uremic ultrafiltrate with a MW between 1 and 5 kD inhibit appetite and suppress food intake in animals.
- A 500 to 2000 D subfraction of uremic serum inhibits apolipoprotein (apo) A-I secretion.

- A compound of MW between 750 and 900 D inhibits osteoblast mitogenesis.
- By now, more than 20 compounds have been identified that conform to the strict definition of middle molecules. Several of those have biological effects, especially a pro-inflammatory impact.
- Dialysis membranes with a capacity to remove middle molecules (high flux membranes) have been related to lower morbidity and mortality.

1) Beta2-microglobulin — (ß2M)

- (MW of approximately 12,000 D) is a component of the major histocompatibility antigen.
- Dialysis-related amyloid, which can be observed in patients being maintained on long-term dialysis, is to a large extent composed of ß2M.
- AGE-modified ß2M has been identified in amyloid of hemodialyzed patients ; it also enhances monocytic migration and cytokine secretion , suggesting that foci containing AGE-ß2M may initiate inflammatory response, leading to bone/joint destruction.
- Serum ß2M levels may be lower in peritoneal dialysis (PD) patients than in hemodialysis patients. This may be due to a better conservation of endogenous residual renal function with PD, since PD alone poorly clears ß2-microglobulin.

- In prospective studies, a progressive decline of predialysis ß2M-levels has frequently been demonstrated in patients dialyzed with membranes with a larger pore size.

- Because ß2M is only removed by dialyzers with large pore size, it may be representative of other large molecules in its kinetic behavior. Apart from its role in amyloidosis, the biological impact of ß2M seems minor.

- Each 10 mg/L increase in predialysis level being associated with an 11 percent increase for all-cause mortality (propably due to infection).

2) Parathyroid hormone

- MW of approximately 9000 D, its increase in concentration during ESRD is attributable to enhanced glandular secretion, rather than to decreased removal by the kidneys. Excess PTH gives rise to an increase in intracellular calcium, resulting in disturbances in the function of virtually every organ system.

- A downregulation of PTH/PTHrP receptor mRNA expression is observed in the liver, kidney, and heart with advanced chronic renal failure, thereby blunting the cellular response to excess PTH and creating resistance to PTH.

- The increased PTH concentration in uremia is the result of a number of compensatory homeostatic mechanisms; phosphate retention, decreased production of calcitriol and hypocalcemia.

3) Advanced glycosylation end products

- (MW 2000 to 6000 D), among the postulated structures for AGE are imidazolone, pyrrole aldehyde.
- The increased accumulation of AGE is not the result of enhanced glucose levels or reduced removal of modified proteins by glomerular filtration.
- With uremia, it is more likely due to increased concentrations of small carbonyl precursors. Thus, uremia can be described as a status of increased carbonyl stress, resulting from increased oxidation or decreased detoxification of these carbonyl compounds.

- AGE products affect multiple processes. These compounds:

1. Cause an inflammatory reaction in monocytes by the induction of IL-6, TNF-alpha, and interferon-gamma.

2. Modify ß2M, which (as previously mentioned) may play an important role in the formation of dialysis-related amyloid.

3. React with and chemically inactivate nitric oxide (NO), a potent endothelium-derived vasodilator, antiaggregant, and antiproliferative factor.

4. Induce oxidative protein modification.

5. In addition to renal failure, AGE products are also retained in diabetes mellitus and aging, settings in which they have been implicated in tissue damage and functional disturbances. Specific receptors for AGE products have also been identified (RAGE), with their expression being enhanced during moderate uremia

- **5) Leptin**, a 16 kD plasma protein that suppresses appetite is retained in renal failure. The increase in serum leptin levels is almost entirely due to a rise in free (non-protein-bound) concentration ; it has been suggested to play a role in the decreased appetite of uremic patients.

- **6) The dinucleoside polyphosphates** (MW1000 Dalton), and are protein-bound. The diadenosine polyphosphates induce proliferation of smooth muscle cells. Uridine adenosine tetraphosphate is a strong vasoconstrictor, which is released by endothelin.

- **7) Others**: Complement factor D, adrenomedullin, atrial natriuretic peptide (ANP), ghrelin, resistin, immunoglobulin light chains, neuropeptide Y, and various cytokines.

GENERAL REMOVAL STRATEGIES

- Conventional hemodialysis and peritoneal dialysis.
- However, dialysis is nonspecific and also removes essential compounds. In addition, lipophilic compounds, which may be responsible at least in part for functional alterations in uremia, are inadequately removed by current dialysis strategies.
- With maintenance hemodialysis, treatment with high flux membranes was suggested to provide superior removal of middle molecules, possibly resulting in improved survival.

- Adding convection by increasing ultrafiltration and equivoluminous substitution with sterile saline or ultrapure dialysate (hemodiafiltration), further adds to middle molecule removal.

- Lower morbidity and mortality are observed in patients submitted to long dialysis sessions.

- Compounds may be cleared more efficiently with continuous or long-lasting low efficiency strategies, because removal is more gradual.

- Optimal removal for each type of molecule may be obtained with a different type of extracorporeal treatment, eg, by using large pore membranes and/or dialyzers or devices with a high adsorptive capacity for some or several of the uremic toxins.

- Removal is also influenced by intestinal intake and preservation of renal function:

1. Intestinal uptake can be reduced by influencing dietary uptake, or by oral administration of absorbents.

2. Preservation of residual renal function may also be an important manner to pursue additional removal of retention solutes.

- Finally, it should be considered that in uremia, not only strategies decreasing solute concentration are important, but interventions countering their biological impact also play a role.


THANK YOU